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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/786,850	02/24/2004	Allan Svendsen	10203.204-US	3589
25908	7590	09/29/2005	EXAMINER	
NOVOZYMES NORTH AMERICA, INC. 500 FIFTH AVENUE SUITE 1600 NEW YORK, NY 10110			MOORE, WILLIAM W	
			ART UNIT	PAPER NUMBER
			1656	

DATE MAILED: 09/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/786,850

Applicant(s)

SVENDSEN ET AL.

Examiner

William W. Moore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 July 2004.
2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,19,20 and 24 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1,2,19,20 and 24 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 24 February 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 20040706.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Restriction

Restriction to one of the following inventions is required under 35 U.S.C. § 121 because this application contains claims directed to the following patentably distinct species of the claimed invention:

Claims 1, 2, 19, 20 and 24 are generic to a plurality of disclosed patentably distinct protease species comprising over 2×10^{38} single and multiple modifications - where 19 amino acid substitutions, an amino acid insertion, or an amino acid deletion are the available modifications - at the 44 separate positions in the amino acid sequence of the mature TY145 subtilase indicated in claim 19, the far more numerous modifications at the 60 positions indicated in claim 20 and the even more numerous modifications at the 83 positions indicated in claim 24. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103(a) of the other invention.

Election

During a telephone conversation with Mr. Elias Lambiris on 7 September 2005 a provisional election was made **with** traverse to prosecute the invention of the specific substitutions at the subtilisin TY145-correspondent positions 171 recited in claim 19. Affirmation of this election must be made by applicant in replying to this Office action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee withdrawn required under 37 CFR 1.17(i).

Priority

Applicant's claim to priority under 35 U.S.C. §§ 119 and 365 to the priority of the 30 January and 7 May 2003 filing dates of Danish Patent Applications, respectively, 2003

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00119 and 2003 006899 which are the basis for the International patent application PCT/DK04/00066 of which the instant application is a divisional filing, is acknowledged, and Applicant's further claim to domestic priority of the 5 February and 7 May 2003 filing dates of the US provisional applications, respectively, serial Nos. 60/445,300 and 60/468,574 is also acknowledged.

Preliminary Amendment

Applicant's Preliminary Amendment filed with the application on 24 February 2004 has been entered and claims 3-18, 21-23 and 24-47 were canceled at Applicant's request. The subject matters of the pending claims 1, 2, 19, 20, and 24 are described by the corresponding claims 1, 2, 19, 20, and 25 presented in Applicant's foreign-filed priority document, the Danish Patent Application 2003 00119, thus enjoy the priority of that application's 30 January 2003 filing date.

Information Disclosure Statement

Applicant's Information Disclosure Statement [IDS] filed 6 July 2004 is hereby acknowledged.

Specification

Compliance with 37 CFR § 1.821 is required in response to this Office action. 37 CFR § 1.821 requires that descriptions of defined nucleotide and amino acid sequences embedded in the specification be accompanied by sequence identifiers properly stated as "SEQ ID NO:n", where "n" is an integer corresponding to the Sequence Disclosure. See 37 CFR §§ 1.821(b), (c) and (d). Examples of portions of the specification that do not comply with 37 CFR § 1.821 include, *inter alia*, the Drawing Description at page 4, lines 20-31 at page 9, and lines 15-17 at page 10.

Claim Objections

Claims 2 19, 20, and 24 are objected to because of the following informalities: Claim 2 is objected to for the lack of number agreement in its preamble between the

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subject, "positions" and the verb "is"; and further objected to because clauses (a), (b), and (c) of the claim lack the appropriate use of the definite article, "the", at the opening of each of subclauses (i)–(iv), see, e.g., the failure of subclauses (i) to state "the Asp c-alpha atom". Each of the independent claims 19, 20 and 24 are objected to for the lack of particular descriptive structures, e.g., clause designations such as those employed in claim 2, that set off separate mobile regions stated at separate lines in claims 19, 20 and 24, and twice in consecutive lines in claim 24. Claim 24 also lacks the preposition "of" before the word "regions" in its terminal clause. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 19, 20, and 24 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the preparation of the divergent subtilases of claims 1, 2, 19, 20, and 24 where claims 1 and 2 reach generic proteases that differ at least at as many as 37% of the positions, i.e., 115 positions overall, from the 311-amino acid sequence of the mature TY145 subtilase set forth in SEQ ID NO:1, and where claims 19, 20 and 24 reach generic proteases that may differ to even greater extent - indeed to an undefined extent - from the amino acid sequence of the mature TY145 subtilase set forth in SEQ ID NO:1 because claims 19, 20 and 24 require no particular reference sequence for determining divergence. The rejected claims fail to describe where the differences occur, and/or what the differences might be and the specification does not otherwise disclose or suggest the nature or source of any of the generic proteins that meet the limitations of the claims. "While one does not need to

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have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification provides no relevant identifying characteristics of proteases of claims 1 and 2 that diverge at as least as many as 115 of the amino acid positions from the 311-amino acid sequence of SEQ ID NO:1, nor relevant identifying characteristics of proteases of claims 19, 20, and 24 that diverge at perhaps as many as, and perhaps more than, 115 of the amino acid positions of the amino acid sequence of an unidentified "TY145-like subtilase". The claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the structure, or other properties, of claimed subtilases.

Claims 1, 2, 19, 20, and 24 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for altering the amino acid sequence of SEQ ID NO:1 by one or a few amino acid substitutions or deletions at positions recited in claims 19, 20 and 24, does not reasonably provide enablement for altering the amino acid sequence of SEQ ID NO:1, or an unidentified amino acid sequence at as many as 115 unassigned positions, or even at as many as the 151 assigned positions indicated in the group of claims 19, 20, and 24. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

If the phrase "homologous to" in claim 1 is construed according to its most limited meaning, positional identity, claims 1 and 2 contemplate arbitrary assignments of any of amino acid substitutions, additions or deletions at as many as 115 positions within the TY145 protease amino acid sequence of SEQ ID NO:1. Claims 19, 20, and 24 contemplate arbitrary assignments of any of amino acid substitutions, additions or deletions at an undefined number of amino acid within unspecified amino acid sequence that need not be similar of SEQ ID NO:1 before alteration, and fail to coordinate any of the 44 positions enumerated in claim 19, any of the 60 positions in claim 20, or any of the 83 positions in claim 24 - amounting to 151 different positions in all - with the particular amino acid sequence of any protease, whether a precursor protease,

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protease, or mature protease amino acid sequence. Indeed, neither the prior art made of record herewith nor Applicant's specification can identify, taken together, 115 undesignated, or 151 designated, amino acid positions that might be concurrently altered in any subtilase amino acid sequence, nor teach the nature of such concurrent alterations that may be made, which permits a resulting modified product to function as a protease. Mere sequence perturbation cannot enable the design and preparation of nucleotide sequences encoding a myriad of divergent subtilases and provide the public with a modified subtilase that retains proteolytic activity.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (discussing eight factors relevant to the analysis of enablement). Applying the factors discussed in *Wands* to Applicant's disclosure, it is apparent that:

- a) the specification lacks adequate, specific, guidance for altering, at least, the amino acid sequence of the mature TY145 subtilase of SEQ ID NO:1 to the extent embraced in any claims 1, 2, 19, 20, or 24,
- b) the specification lacks working examples wherein the subtilase having at least the amino acid sequence of SEQ ID NO:1 is altered to the extent embraced in the claims,
- c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,
- d) unpredictability exists in the art where no members of the class of mature subtilase amino acid sequence represented by, at least, the amino acid sequence of SEQ ID NO:1 have had as many as 115, let alone 151, amino acids concurrently modified.

Thus the scope of subject matters embraced by the phrase, "at least 63% homologous thereto", is unsupported by the present specification even if taken in combination with teachings available in the prior art.

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The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 19, 20, and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 19, 20, and 24 are indefinite because each is narrative in form and replete with indefinite, functional, language, e.g., "TY145 like", "positions of . . . ion-binding sites in the three-dimensional structure . . . defined by distance", but not by direction, "overall subtilisin fold", "Strong ion binding site . . . not present", "highly mobile region", "mobile region", and "sub-region". Amending the claims to require modification of a specific subtilase amino acid sequence, e.g., the sequence set forth in SEQ ID NO:1, as well as to organize and correlate tertiary structural features indicated in clauses (a)-(c) of claims 1 and 2, and to correlate positions enumerated in claims 19, 20, and 24, with the reference sequence will overcome this aspect of the rejection.

Claim 1 is further indefinite in reciting, "TY145 like subtilase", in its preamble and then reciting an exclusion of four subtilases in its final clause because no single, altered, reference subtilase amino acid sequence is required by the claim and no specific amino acid sequence is identified for subtilases to be excluded, e.g., as by the identification of SEQ ID NO:1 itself or any of SEQ IDs NOs:2-4, where such designations are arbitrary and no subtilase, no matter what words are applied to describe it, knows from whence it came. Claim 2 is included in this rejection because it depends from claim 1 but fails to clarify the ambiguity of the independent claim.

Claims 19, 20, and 24 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite in that each fails to point out what is included or excluded by the claim language. While the claims recite enumerate positions for unspecified alterations, the preamble of each claim, in reciting "[a] TY145 like subtilase variant", indicates that an alteration at a numbered position may occur in a protease amino acid sequence already altered, thus each of claims 19, 20 and 24 is an omnibus type claim. Amending each

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claim to set forth numbered positions registered according to a specific amino acid sequence, see, e.g., claim 1 which requires correspondence with the sequence of SEQ ID NO:1, and stating the positions in a proper Markush format utilizing the phrase "selected from the group of positions consisting of", where the "regions" are set off by appropriate designations and the final region is linked by the conjunction "and" to the preceding region, will overcome this rejection.

Claims 20 and 24 are further rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because both recite a broad range or limitation together with a narrow range or limitation, introduced by the term "preferably", that falls within the broad range or limitation. This is indefinite because the resulting claims cannot clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is either merely exemplary of the remainder of the claim, and therefore not required, or a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). This rejection may be overcome by deleting the narrower range or limitation from the claims and presenting the narrower range or limitation from either claim in a further, dependent, claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

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(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 2, 19, 20, and 24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Servant et al., 1999, and the amino acid sequence of UniProt Accession No. Q9S3L6, 2000, both made of record herewith.

Servant et al. disclose a subtilase amino acid sequence sharing 73.5% identity with SEQ ID NO:1 herein, see UniProt Accession No. Q9S3L6, wherein amino acids present at many positions recited in claims 19, 20, and 24 - including those present at subtilisin TY145-correspondent positions 1-3, 4, 7, 17-20, 22, 39, 43, 46-49, 57-64, 70, 87-89, 107, 109, 124, 127, 129, 130, 146, 147, 151, 155, 159, 212-214, 220, 241, 265, 266, 269, 278, 279, 282, 286, 287, and 293 - constitute substitution modifications of SEQ ID NO:1 herein, meeting one or more structural limitations of claims 1, 2, 19, 20, and 24.

Claims 1, 2, 19, 20, and 24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wati et al., UniProt Accession No. O54327, 1998, made of record herewith.

Wati et al. disclose a subtilase amino acid sequence sharing 73.0% identity with SEQ ID NO:1 herein, see UniProt Accession No. Q9S3L6, wherein amino acids present at many positions recited in claims 19, 20, and 24 - including those present at subtilisin TY145-correspondent positions 1-3, 4, 7, 17-20, 22, 39, 43, 46-49, 57-64, 70, 87-89, 107, 109, 124, 127, 129, 130, 146, 147, 151, 155, 159, 212-214, 220, 241, 265, 266, 269, 278, 279, 282, 286, 287, and 293 - constitute substitution modifications of SEQ ID NO:1 herein, meeting at least one structural limitation of claims 1, 2, 19, 20, and 24.

Claims 1, 2, 19, 20, and 24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Davail et al., 1992, made of record with Applicant's IDS filed 6 July 2004.

Davail et al. disclose a subtilase amino acid sequence sharing 68.1% identity with SEQ ID NO:1 herein, see Figure 4 at page 17450, wherein amino acids present at many the positions recited in claims 19, 20, and 24 - including those present at the subtilisin TY145-correspondent positions 1-3, 5, 6, 17-20, 22, 39, 43, 46-49, 57-64, 70, 87-89, 107, 109, 124, 127, 129, 130, 146, 147, 151, 155, 159, 212-214, 220, 241, 265, 266,

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269, 278, 279, 282, 286, 287, and 293 - constitute substitution modifications of SEQ ID NO:1 herein, meeting one or more structural limitations of claims 1, 2, 19, 20, and 24.

Claims 1, 2, 19, 20, and 24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Narinx et al., 1992, made of record with Applicant's IDS filed 6 July 2004.

Narinx et al. disclose a subtilase amino acid sequence sharing 65.5% identity with SEQ ID NO:1 herein, see Figure 4 at page 1275, wherein amino acids present at many positions recited in claims 19, 20, and 24 - including those present at subtilisin TY145-correspondent positions 1-3, 4, 7, 17-20, 22, 39, 43, 46-49, 57-64, 70, 87-89, 107, 109, 124, 127, 129, 130, 146, 147, 151, 155, 159, 212-214, 220, 241, 265, 266, 269, 278, 279, 282, 286, 287, and 293 - constitute substitution modifications of SEQ ID NO:1 herein, meeting one or more structural limitations of claims 1, 2, 19, 20, and 24. Narinx et al. further disclose, in the full paragraph of the left column of page 1275, making specific amino acid substitutions at the subtilisin TY145-correspondent positions 69, 86, 108, 123, and 292, meeting further limitations of claims 20 and 24.

Claims 1, 2, 19, 20, and 24 are rejected under 35 U.S.C. § 102(b) as being anticipated by Miyazaki et al., 1990, made of record with Applicant's IDS filed 6 July 2004.

Miyazaki et al. disclose a subtilase amino acid sequence sharing 68.1% identity with SEQ ID NO:1 herein, see the sequence of first rows across Figure 1 at page 1017, wherein amino acids present at many positions recited in claims 19, 20, and 24 - including those present at subtilisin TY145-correspondent positions 1-3, 5, 6, 18-20, 22, 39, 43, 46-49, 57-64, 70, 87-89, 107, 109, 124, 127, 129, 130, 146, 147, 151, 155, 159, 212-214, 220, 241, 265, 266, 269, 278, 279, 282, 286, 287, and 293 - constitute substitution modifications of SEQ ID NO:1 herein, meeting one or more structural limitations of claims 1, 2, 19, 20, and 24. Miyazaki et al. further disclose, see Figure 2 at page 1018, making specific amino acid substitutions at the subtilisin TY145-correspondent positions 17, 146, 213, 214, 276, and 293, meeting further limitations of claims 19, 20 and 24.

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Claims 1 and 2 are rejected under 35 U.S.C. § 102(e) as being anticipated by Outtrup et al., US 6,511,371, made of record herewith.

Outtrup et al. disclose a subtilase amino acid sequence, see SEQ ID NO:2, which is identical to SEQ ID NO:1 herein, meeting limitations of claims 1 and 2 herein.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Ponnathapura Achutamurthy, can be reached at 571.272.0928. The fax phone number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
23 September 2005


KATHLEEN M. KERR, PH.D.
SUPERVISORY PATENT EXAMINER